Medical Progress

Local and Systemic Factors in the Pathogenesis of Thrombosis

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THE PURPOSE OF THIS REPORT is to develop a formulation of the pathogenesis of thrombosis in which three entities are separated from each other —the arterial thrombus, the red (stasis) thrombus, and the syndrome of disseminated intravascular coagulation. Each of these forms of thrombosis has distinct pathophysiologic features, arising from distortions of different segments of the normal hemostatic sequence. In each there is a different balance between local and systemic factors predisposing to vascular occlusion, and in each there is a characteristic response to anticoagulant therapy.

Clarification of the pathogenesis of thrombosis has emerged from a rapid expansion of knowledge of the normal hemostatic process. During the past decade, as a result of detailed electronmicroscopic studies of hemostatic plug formation, and as a consequence of entirely new concepts of platelet aggregation mechanisms, there has been a shift in the theory of the hemostatic process.[1,2] Previously, most investigators believed that the hemostatic mechanism was in continuous operation; that there was continued deposition of fibrin on normal vessel walls, thereby maintaining vascular structural integrity; and that the rapid turnover of most coagulation factors reflected the consumption of clotting proteins during this continuous process. As Hjort[2] has emphasized, the central assumption of this viewpoint was that the hemostatic mechanism presumably acted at all times upon normal, uninjured endothelium, and that local tissue injury served merely to accelerate an otherwise slowly operative process. It is now recognized, however, that the normal hemostatic process is in fact not continuously operative. Rather, it is essentially an intermittent process, activated only in response to local injury. Accumulated evidence discounts the concept that the turnover of clotting factors reflects their utilization during normal hemostasis. The fundamental new concept is that the hemostatic process is not operative on normal endothelium, but requires a "structural trigger"[3] to initiate hemostasis. That trigger is injury to the vascular endothelium.

The Normal Hemostatic Mechanism

The normal hemostatic process begins when a blood vessel is injured and culminates in the formation of a fibrin-platelet meshwork that is a structural barrier to the escape of blood at the site of injury.[4] The most immediate and direct response to injury is vascular constriction.[5-8] The hemostatic significance of vascular constriction is

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intuitively apparent, for if a vascular bed that cannot constrict is transected (for example, the telangectatic vessels in Osler-Weber-Rendue disease) prolonged and profuse bleeding results even if all other components of the hemostatic mechanism are intact. Although a few studies of this most fundamental response to injury have been made, the mechanisms whereby vessel injury provokes vasoconstriction are largely uncharacterized.

The trigger that initiates subsequent hemostatic reactions is the separation or disruption of the endothelium, thereby allowing flowing blood to contact subendothelial connective tissue. At once, the platelets immediately adjacent to the site of injury adhere to the connective tissue, and, rapidly, additional platelets brought to the site of injury by the flowing blood form large aggregates which extend from the site of injury into the blood vessel lumen, forming the initial or temporary hemostatic plug.

New knowledge of the mechanisms by which the temporary hemostatic plug is formed represents a major advance in our understanding of hemostasis and has greatly clarified our concepts of the pathogenesis of thrombosis. That collagen was the specific component of connective tissue to which platelets adhere was first suggested by Hugues[9-11] and by Bounameaux.[12] This proposition was repeatedly confirmed in other laboratories.[13-15] It is now established that the adherence of platelets to collagen is independent of ionized calcium,[13,16] that no plasma cofactors are required,[13,16] that the maintenance of the native triple helical structure of collagen is essential,[17] but that removal of negatively charged telopeptides by pepsin does not affect platelet adherence.[17,18] Furthermore, blockage of free amino groups of lysine profoundly diminishes the reactivity of collagen with platelets, whereas acetylation of the carboxyl groups of collagen does not interfere with platelet adherence.[17]

The stimulus that leads to the piling up of aggregated masses of platelets extending away from the site of injury into the vascular lumen has also been clarified. The essential mediator of this process is the nucleotide adenosine diphosphate (ADP). That ADP could aggregate platelets was first established by Hellem[19] and by Gaarder[20] and her associates. Subsequent studies have shown that as platelets adhere to collagen,[16,21,22] they release ADP; that the amount of ADP released is sufficient to cause further aggregation of platelets[23]; and that the aggregation of platelets caused by epinephrine[24] and thrombin[25] is also ADP-mediated. When radioactive phosphate or adenosine are incubated with platelets, they are incorporated into platelet nucleotides, including ADP. When such labelled platelets are aggregated by collagen or by thrombin, release of ADP is readily detectable by chemical assays, but no radioactive nucleotides are released.[22,26] These studies indicate that two pools of ADP exist in the platelet and that release of ADP occurs from only one of them. In contrast to the collagen-initiated reaction, ADP-induced platelet aggregation occurs only in the presence of divalent cations,[27-29] and requires fibrinogen and a heat-stable plasma protein for maximal aggregation to occur.[30-33]

Recently, several drugs have been found which can selectively interfere with the sequence involved in platelet aggregation. Thus, aspirin[34-37] and the pyrazole[38] compounds such as phenylbutazone block the release of ADP by collagen, epinephrine, and by ADP itself. Furthermore, the vasodilator dipyridamole directly inhibits the aggregation reaction caused by ADP.[24] In addition familial disorders[39-43] have been described in which the platelet release of ADP in response to aggregating reagents is impaired as a hereditary defect. Thus, the selective defects either inherited or induced by drugs emphasize the sequence of the initial reaction in the hemostatic process.

The ultrastructural changes that accompany platelet aggregation reactions have been extensively studied.[44-49] Platelets circulate normally as ovoid discs. Immediately underneath their plasma membrane, platelets contain a marginal band of microtubules which appear to be under some degree of centrifugal tension. It has been postulated that this marginal band of microtubules maintains the disc-like shape of the platelets. Platelets also contain mitochondria, lysosomal granules, and glycogen. When platelets contact collagen, striking changes occur. The platelets swell, the marginal band of tubules is disrupted, and the lysosomal granules and mitochondria disintegrate. In contrast, when the platelets aggregate in response to ADP, they swell, but the marginal band of microtubules is now found in the interior of the cell where it tightly surrounds intact, closely approximated lysosomal granules and mitochondria.

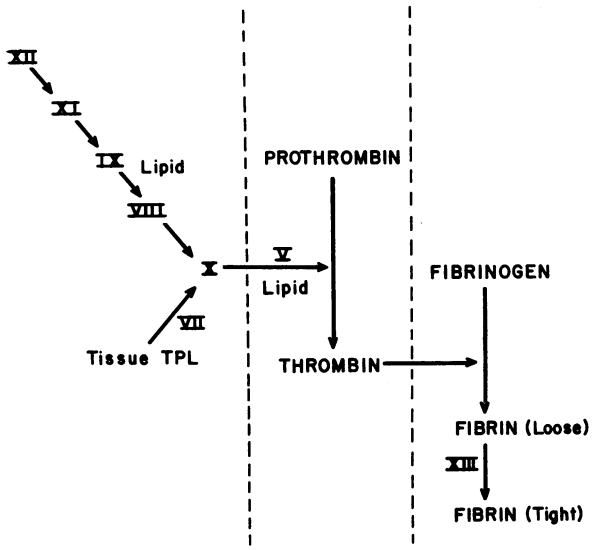

Chart 1.—The Clotting Sequence. Nomenclature: Factor XII=Hageman; Factor XI=Plasma Thromboplastin Antecedant (PTA); Factor IX=Plasma Thromboplastin Component (PTC, Christmas Factor); Factor VIII=Antihemophilic Factor (AHF); Factor X=Stuart Factor; Factor VII =Serum Prothrombin Conversion Accelerator (SPCA); Factor II=Prothrombin; Factor V=Proaccelerin; Factor I=Fibrinogen; Factor XIII=Fibrin Stabilizing Factor.

NOTE: All steps subsequent to the activation of XI by XII require ionized calcium.

The subsequent steps in the hemostatic process involve the transformation of the temporary hemostatic plug, formed by the loose platelet aggregates, into a permanent plug stabilized by fibrin. This transformation is brought about by activation of the blood clotting mechanism. The critical steps in this sequence are the conversion of prothrombin to thrombin and the subsequent conversion of the soluble protein fibrinogen to an insoluble polymer of fibrin.

There are two major pathways by which prothrombin is converted to thrombin. The first of these, the so-called "intrinsic pathway," is initiated by the conversion of Hageman factor or factor XII from an inert precursor to an activated form.[50] *In vitro,* substances that have electronegatively charged, wettable surfaces are capable of transforming the Hageman factor.[51,52] Such surfaces include glass and collagen fibers.[53] It is probable that in the injured vessel, exposure of collagen to the plasma proteins is the initial step in the activation of the intrinsic pathway. Recent studies have shown that the presence of free carboxyl groups is essential for collagen-induced transformation of Hageman factor.[53]

Once factor XII is activated, it initiates a series of reactions that have been described as a waterfall[54] or cascade[55] in which certain blood clotting factors are sequentially converted from their inactive or precursor form to their active or enzymatic form (Chart 1). Thus, activated factor XII activates factor XI (PTA), which in turn activates factor IX (PTC or the Christmas factor). The reaction between activated factor IX, factor VIII (the anti-hemophilic factor) and factor X (Stuart factor) is a complex one. It is not yet certain whether factor IX activates factor VIII, which in turn activates factor X, or whether activated factors IX, VIII and platelet lipids together form a complex which activates factor X. Activated factor X in the presence of coagulation factor V and phospholipid (derived from platelets) converts prothrombin to thrombin. Thrombin then converts fibrinogen to fibrin monomer, which spontaneously polymerizes. However, this polymer is a loose and easily dissociated aggregate held together only by hydrogen bonding. Yet another clotting factor, factor XIII[56] or the fibrin stabilizing factor, converts the hydrogen bonds to covalent links, forming the dense, tight fibrin that is the final product of the coagulation sequence.

The "extrinsic pathway" is a second mechanism which activates prothrombin. Many tissues, particularly blood vessel walls, lung and brain, contain a microsomal lipid-protein complex called tissue thromboplastin which is directly capable of activating factor X in the presence of an accessory cofactor, factor VII.[57,58] Activated factor X then reacts in an identical fashion to that already described and converts prothrombin to thrombin. In this pathway, however, the lipid required for the conversion of prothrombin is derived from the tissue thromboplastin itself and platelet lipids are not required.

As a result of the activation of both pathways of the clotting mechanism, thrombin is produced explosively at the site of tissue injury. If unchecked, the local production of thrombin could theoretically lead to massive systemic defibrination, for there exists in 15 ml of blood sufficient potential thrombin (if prothrombin were completely converted to thrombin) to clot 2,500 ml of plasma in 15 seconds. Clearly, there are efficient mechanisms which limit the hemostatic process and confine it to the site of local injury. Several kinds of limiting reactions are operative: those that re-

tard the formation of thrombin; those that block the reaction of thrombin and fibrinogen; those that affect the conversion of fibrinogen to fibrin; and the effects of rapid blood flow.

There is in blood a series of inactivators which progressively impede the procoagulant activity of each of the precursors of prothrombin.[59-61] Thus, when shed blood clots in siliconized test tubes *in vitro,* certain of the thrombin precursors disappear from the resulting serum. Although the levels of factors XII, XI, IX and X remain relatively unaltered, factor VIII and factor V activity in serum is greatly depressed. However, if shed blood is clotted in the presence of potent activators of the contact system, the content of factors IX, X, and XI in the serum is greatly reduced. Finally, if shed blood is clotted in the presence of tissue thromboplastin, the resulting serum contains little factor X activity, but the levels of factors XII, XI, and IX are unaltered. These observations may be rationalized by the concept that the disappearance of clotting factor activity in shed blood reflects the selective inactivation of the activated, rather than the inert or precursor form of the procoagulants. Under conditions which favor maximal activation of a procoagulant, its activity will be selectively depressed in serum. However, since the inactivation of factors V and VIII is primarily influenced by the presence of thrombin, depression of these two factors will be present in all circumstances in which shed blood is allowed to clot. The blood inactivators of thrombin precursors share another property: the rate of inactivation of an activated clotting intermediate is relatively slow. In recent experiments we demonstrated that the apparent *in vitro* half-time of decay of activated factor X in serum exceeded 50 minutes.[62]

In addition to the blood inhibitors, there are efficient tissue mechanisms that also participate in the removal of activated clotting factors. The clearance of activated procoagulants from the circulation was first demonstrated by Spaet and Kropatkin[63] in 1958. They demonstrated that intravenously injected soluble blood thromboplastin precursors were ineffective in producing the defibrination syndrome, and they suggested that a cellular clearance mechanism might be operative in the removal of activated procoagulants. In subsequent studies Spaet and his associates demonstrated that the reticuloendothelial system removes particulate blood thromboplastin, and that liver removes activated factor X formed by the operation of the intrinsic coagulation mechanism.[64] In other studies from our laboratory we have also demonstrated that factor X, activated either by trypsin or by Russell's viper venom, was removed by the liver with an apparent half-time of approximately seven minutes.[62] The mechanism of hepatic cellular clearance of activated procoagulants has not been established. It has been demonstrated that there is no release of an hepatic inhibitor,[64,65] but whether the attenuation of activated factor IX or X activity that can be demonstrated upon perfusion of these activated precursors through isolated liver preparations represents interhepatic degradation of procoagulants or interhepatic binding of the procoagulants is not yet clear.

In our experiments,[65] intense activation of the intrinsic system *in vivo* was produced by the infusion of thrombin-free serum into rabbits. In these experiments infusion of serum directly into the portal vein was far less effective in producing systemic hypercoagulability than was infusion of serum into a peripheral vein. Furthermore, when serum was infused into animals in which the hepatic circulation was occluded, widespread thrombosis occurred in all major vascular systems. These studies demonstrated that the liver played a key role in the attenuation of the hypercoagulable response to serum. These observations have been extended by the finding that during liver transplantation, striking acceleration of intravascular coagulation becomes apparent when the liver is removed from the circulation.[66]

The inactivation of clotting factors has been demonstrated primarily in shed blood. During normal hemostasis, the levels of circulating procoagulants remains unaltered. Conversely, the role of the hepatic clearance mechanism has been demonstrated in experiments in which there has been systemic rather than local stimulation of the coagulation mechanism. Therefore, the relative role of these two mechanisms in limiting the growth of the normal hemostatic plug has not yet been established.

When thrombin is added to plasma, it is rapidly neutralized. As many as six different antithrombic activities (each with a different Roman numeral) have been described. However, it is now clear that there are only two major mechanisms by which thrombin is neutralized during the normal hemostatic process. The first of these is the physical

removal of thrombin from the solution by adsorption to fibrin.[67] It has been demonstrated that fibrin rapidly binds a large excess of thrombin and that this adsorption accounts for the major portion of the rapid disappearance of thrombin when it is added to plasma. The adsorptive capacity of fibrin for thrombin has been given the term antithrombin I.

Another mechanism is also operative, for thrombin is also neutraliezd when it is added to defibrinogenated blood or to serum. In contrast to the immediate removal of thrombin by adsorption to fibrin, the neutralization of thrombin in defibrinogenated plasma is a time-consuming process. The activity responsible for the progressive inactivation of thrombin in serum or plasma has been termed antithrombin III.[68] It has been recently demonstrated that progressive antithrombin directly interferes with the ability of thrombin to release fibrinopeptides from fibrinogen.[69] Antithrombin does not influence the subsequent polymerization of fibrin monomer. In addition, the same protein that is responsible for the progressive inactivation of thrombin also appears to be identical with the cofactor required for the antithrombic action of heparin (previously termed antithrombin II).

The relative importance of thrombin adsorption and thrombin inactivation in the normal hemostatic process has not been established. At least one investigator[70] believes that adsorption represents the only significant physiologic process, but others[71,72] feel that both adsorption and inactivation are physiologically operative. One observation that emphasizes the importance of progressive antithrombin is a description of a kindred with a defective progressive antithrombin activity.[73] In this family there was a high incidence of thromboembolic disorders.

The fibrinolytic system plays a major role in the maintenance of the fluidity of the blood, particularly in the small vessels. Vascular endothelium contains a potent tissue activator which converts an inert protein plasminogen into the potent enzyme plasmin. Unlike thrombin, plasmin is rather non-specific. It digests factors V, VIII, fibrin, fibrinogen itself, and certain of the components of complement.[74] The tissue activators of plasminogen are released from blood vessel walls by injury or by anoxia.[75] Furthermore, activated factor XII and thrombin itself can also convert plasminogen to plasmin.[76] Thus, activation of the fibrinolytic mechanism inevitably is linked to the activation of the hemostatic process and must be considered an integral component of hemostasis. It has been shown that there is an inverse relationship between vessel size and fibrinolytic activity.[77] Recent studies have demonstrated the resistance of small vessels to occlusive thrombus formation.[78] When systemic hypercoagulability was produced in rats by the infusion of serum, occlusive thrombi formed in isolated large vein segments. No thrombus formation was observed, however, in veins with a diameter of less than 50 microns. Pretreatment of rats with epsilon-amino caproic acid before the infusion of serum resulted in fibrin deposition in all the small veins and enhanced thrombus formation in the larger vessels as well. These observations emphasize the function of the fibrinolytic system in preventing occlusive thrombus formation in small vessels.

The mechanism by which activation of plasminogen maintains the fluidity of blood in small vessels may be largely a reflection of the elaboration of inhibitors of fibrin polymerization and of the thrombin-fibrinogen reaction.[79,80] When plasmin reacts with fibrinogen, a sequential degradation of the fibrinogen molecule occurs. If the reaction is allowed to proceed to completion *in vitro,* three classes of fragments are produced: one with a molecular weight of approximately 88,000; a second with a molecular weight of approximately 30,000; and a third heterogeneous group of fragments of lower molecular weight. Although these fragments are not clottable by thrombin (and thus persist in serum) they exert a powerful inhibitory effect on the polymerization of fibrin monomer. They not only retard the rate of fibrin monomer polymerization, but they also become incorporated into the growing fibrin polymer producing a defective, fragile fibrin mesh with a highly abnormal structure. In addition early in the reaction between plasmin and fibrinogen large abnormal fibrinogen fragments are produced. These fragments also are potent anticoagulants. They exert their effect both on the polymerization of fibrin monomer and on the conversion of fibrinogen to fibrin monomer. On a molar weight basis, these early fibrinogen-derived fragments are much more potent than are the late products of plasmin digestion of fibrinogen. Unlike the end products of plasmin-fibrinogen interaction, the early fragments are partially clottable by thrombin, though at a retarded rate. Thus, they are not present in serum.

There are other mechanisms by which activation of the fibrinolytic mechanism may retard thrombus formation. Thus, it has been observed that fibrinogen degradation products interfere with platelet aggregation reactions, and it is known that plasmin degrades factors V, VIII and IX as well as fibrinogen.[74] Whether or not these ancillary effects of plasmin play a significant role in the limiting of the normal hemostatic process has not yet been established.

In addition to those factors already described, the complex effects of blood flow on limiting spread of the hemostatic plug must be considered. Rapid blood flow serves two functions: it dilutes the local concentration of activated blood clotting factors, and it mechanically opposes the spread of the growing platelet mass.

As in the elucidation of the components of the clotting sequence, the participation of each mechanism in the limitation of the unchecked spread of the hemostatic plug is more easily recognized by its absence than by its presence. Thus, the role of the liver in clearing activated coagulation factors is emphasized by the acceleration of intravascular coagulation that occurs when the hepatic circulation is occluded. The role of antithrombin is accentuated by the high incidence of thromboembolic disease in its absence. The normal protective role of the fibrinolytic system is uncovered when inhibitors of fibrinolysis are employed. Finally, the importance of rapid blood flow is emphasized by the importance of vascular stasis in the etiologic derivation of clinical intravascular thrombosis — an observation that has been entrenched since the time of Virchow.

From the foregoing discussions we may now summarize the events that occur in the normal hemostatic response. First, the blood vessel contracts in response to vessel injury. In addition, as the endothelial barrier is broken, subendothelial collagen is exposed to the blood vessel lumen. This exposure to collagen initiates a series of platelet reactions mediated at first by collagen itself and subsequently by adenosine diphosphate, producing an occlusive plug of platelets that extends from the site of vascular injury into the lumen of the contracted blood vessel where it provides the first or temporary barrier to blood loss. Simultaneously, the exposure of collagen to plasma and the release of tissue thromboplastin activate both the intrinsic and extrinsic systems of blood coagulation, resulting in the explosive production of thrombin at the site of vascular injury. In the presence of thrombin the platelet plug undergoes transformation and becomes a non-reversible mass intertwined with fibrin. The process of hemostatic plug formation is limited by a series of complex reactions which include adsorption of thrombin, inhibition of precursors of thrombin and of thrombin itself, hepatic cellular clearance mechanisms, fibrinolytic activation, and rapid blood flow. As a consequence of the balance between hemostatic plug formation and limiting reactions, the circulation is occluded only locally in areas of tissue damage. Tissue ischemia does not ensue, and there are no distant sequelae.

Red (Stasis) Thrombus Formation

Thrombosis cannot readily be defined as a single pathologic entity. To do so results in a viewpoint that rejects all morphologic variants of thrombi that differ from the classic mixed arterial lesion as curiosities and artifacts. Rather, a concept of the pathogenesis of thrombosis more in keeping with our present understanding of the hemostatic sequence recognizes at least three forms of thrombus — the white or arterial thrombus, the red or stasis thrombus, and the syndrome of disseminated intravascular coagulation. The pathophysiologic lineage of each of these processes is determined both by the interplay of local and systemic factors in the *initiation* of the thrombus and by the role of blood flow in the *propagation* of the thrombus. The validity of this distinction is further buttressed by the response of each of these forms to anticoagulant therapy.

Morphologically the thrombus that forms in columns of static blood closely resembles a blood clot formed *in vitro* in a glass tube. It consists primarily of a meshwork of fibrin strands in which the formed elements of the blood are trapped in a random fashion. It is found primarily in the venous tree, or, when found on the arterial side of the circulation, it exists as the propagating red tail distal to an occlusive white thrombus. Unlike the events in the formation of the hemostatic plug, no clear "structural trigger" can be defined which precipitates venous thrombosis. Clearly, in most instances of thrombophlebitis morphologic disruption of the endothelium cannot be identified. Furthermore, in certain clinical settings, for example, malignant lesions of the lung and gastrointestinal tract, the occurrence of multiple episodes of

spontaneous venous occlusion widely separated throughout the venous tree suggests that a systemic stimulus may be capable of initiating venous thrombosis in areas of retarded blood flow. The concept of a systemic "trigger" for thrombosis has derived strong experimental support from laboratory models which have demonstrated that activation of the intrinsic system *in vivo* results in the deposition of red thrombi in areas of stasis.[65,81-83] At the moment there is no clear idea of what the stimuli are that spontaneously activate the intrinsic mechanism in those states that predispose to venous thrombosis. It is not known, for example, whether they arise in the general circulation or locally in areas that are predisposed to thrombosis. It is known, however, that stasis is necessary for the red thrombus to form. Stasis provides two functions: it prevents dilution of activated blood-coagulation factors by blood flow, and it prevents the clearance of activated blood-coagulation factors by the hepatic clearance mechanism. What, then, can one say about the balance between local and systemic factors in the development of venous or stasis thrombus? From clinical and experimental observations it seems likely that at least in some large fraction of spontaneous venous thrombosis a systemic stimulus acts as the trigger. Clearly, however, local stasis determines at which point the venous thrombi form. Thus, activation of the blood clotting system and local stasis together participate in the pathogenesis of the red thrombus.

White (Platelet) Thrombus Formation

The thrombus that forms on the arterial side of the circulation is composed primarily of platelets and fibrin, called by pathologists the white thrombus. It forms almost exclusively in areas of rapid blood flow in association with an injured or abnormal vessel wall, generated in most instances by an atheromatous plaque but in others from other lesions that interrupt the normal endothelial barrier. Although earlier investigators held that intimal injury produced damaged endothelial cells to which platelets adhered, Spaet[3] and French[84] have marshalled impressive evidence that in fact the initiating event in the formation of arterial thrombosis is the denudation of the endothelium and exposure of platelets to subendothelial collagen. Therefore, the "structural trigger" in the formation of arterial thrombosis resembles that in the initiation of the hemostatic plug. It is mediated primarily by platelet reactions with collagen and does not depend primarily on the blood coagulation system.

In contrast to the events in the small vessel the platelet mass is initially non-occlusive since it does not form in a constricted vessel. It grows continuously as the blood stream brings to it a new supply of platelets. Counterbalancing the accretion force, however, is the disruptive force of the axial flow of the blood stream, which sweeps away the most peripheral parts of the newly forming thrombus. Thus, the white thrombus initially tends to be mural in configuration. As the mural thrombus continues to grow, perhaps in association with extension or expansion of the underlying atherosclerotic lesion, circulation in the immediate area slows. In the presence of the locally activated blood-clotting system, areas of stasis or red-thrombus accretion may become intermeshed with a white platelet nidus. These areas then become coated with new platelets from the ambient blood, forming the white lines of Zahn. Finally, as the circulation is completely occluded, thrombus formation proceeds entirely through the red-thrombus mechanism. This sequence then leads to the evolution of the mixed thrombus, the most frequently observed gross pathologic lesion on the arterial side of the circulation. One need not invoke any systemic factors in the production of the arterial thrombus, and, indeed, there is little evidence to suggest that any systemic activation of the blood coagulation system is *primarily* operative in the formation of the arterial thrombus. Thus, the arterial thrombus like the hemostatic plug remains primarily a locally determined phenomenon.

Disseminated Intravascular Coagulation

A third form of thrombosis is the deposition of fibrin in the microvasculature throughout the body, particularly in the liver, kidney, spleen and brain. In man such diffuse deposition of fibrin throughout the body is seen in diverse syndromes including amniotic fluid embolism following incompatible blood transfusion reactions, during the course of malaria, in the retained dead fetus syndrome, in association with malignant disease of either the solid organs or of the blood-forming system, and in Gram-positive septicemia. This generalized and widespread thrombosis is given the descriptive term of disseminated intravascular coagulation. This syndrome was discussed in detail by McKay[85]

in a recent review article in CALIFORNIA MEDICINE. Briefly, it is the result of the release of precoagulant materials into the blood stream. For example, in the retained dead fetus syndrome and in amniotic fluid embolism, thromboplastin is released into the blood stream, thereby activating the extrinsic coagulation system throughout the body. In other syndromes procoagulant material is released which activates the intrinsic system. Whatever the stimulus, as a result of progressive coagulation within the flowing blood stream itself there is marked consumption of certain of the blood clotting factors and in addition there is often activation of the fibrinolytic mechanism. As a result of this complex interaction the whole hemostatic mechanism crumbles and the patient often presents with symptoms of diffuse intravascular occlusion and simultaneously of a widespread bleeding disorder. Whether or not actual fibrin deposition occurs in small vessels reflects a balance between the intensity of the stimulus, the efficiency of hepatic clearance mechanisms, and the degree of activation of the fibrinolytic system. Therefore, in this syndrome the accumulation of fibrin deposits when they occur in the microvasculature is a purely passive phenomenon that reflects a systemic disease process in which local factors are not primarily operative. In this instance the stimulating factor is systemic; it is mediated by the blood clotting system; and it is always a hallmark of some other concomitant disease process.

Anticoagulant Therapy

The response to anticoagulant therapy of each form of thrombosis reflects both the mode of action of anticoagulant drugs and the primary pathologic stimulus to the formation of the thrombus. Direct anticoagulants, such as heparin, block the activation of factor IX and prevent the reaction between thrombin and fibrinogen. The coumarin agents retard the synthesis of factors IX, II, VII, and X. Therefore, the commonly employed anticoagulant agents derive their benefit exclusively from their action on the coagulation mechanism. It has been repeatedly demonstrated that these agents in clinically safe doses have no effect on platelet aggregation reactions and do not block the initial events in the hemostatic sequence — that is, the reactions between platelets and collagen and the aggregation of platelets in response to adenosine phosphate. Furthermore, anticoagulants have no effect on the formation and development of the atherosclerotic plaque.

From these considerations it is clear that anticoagulants cannot be expected to have a significant beneficial role in the prevention of the formation or extension of the white or arterial thrombus. Indeed, critical review of often contradictory literature leads inevitably to the conclusion that there is little to support the concept that anticoagulant agents have had, in fact, a demonstrated therapeutic role in the treatment of the arterial lesion.[86,87] In contrast, there is little doubt that anticoagulation therapy has had a decidedly beneficial role in the prophylaxis and treatment of the red venous thrombus. Controlled studies have demonstrated the efficacy of anticoagulant agents in the treatment of recurrent pulmonary embolism[88] and in the prevention of pulmonary embolic disease in settings in which a high incidence of recurrent venous thrombosis may be expected.[89,90] In addition, in those studies which showed little benefit of anticoagulant therapy in reducing recurring white thrombus formation, there was a striking reduction of venous thrombosis in almost all such studies.[86] Conversely, since the red thrombus originates primarily from an abnormality in the coagulation mechanism it is not surprising that dipyrimidole, which affects

TABLE 1.—*Pathogenesis of Thrombosis*

Type of Thrombus	*Pathogenesis*	*Response to Anticoagulant Therapy*
White Thrombus	Platelet reactions with abnormal vascular wall, in areas of rapid flow. Local factors predominate	No significant response to conventional anticoagulant therapy. Efficacy of anti-platelet agents not yet established.
Red Thrombus	Activated coagulation mechanism in areas of retarded flow. Local factors (stasis) and systemic factors (activating stimulus) operative.	Beneficial response to heparin and coumarins established.
Disseminated Intravascular Coagulation	Diffuse activation of coagulation and fibrinolytic mechanisms. Systemic factors predominate.	May be reversed by heparin.

platelet aggregation reactions, should have no effect in reducing the incidence of clinically detectable deep vein thrombosis.[91] Finally, there is convincing evidence that heparin is the drug of choice in the disseminated intravascular coagulation syndrome. Several studies have shown that there is prompt restitution of fibrinogen to normal levels with return of the platelet count to normal and cessation of bleeding when heparin is given in the course of disseminated intravascular coagulation.[92,93] It is of interest that in the therapy of this disease process which reflects an intense activation of the entire coagulation syndrome, the coumarin agents have been shown to be less effective than heparin.[93] These observations — ineffectiveness of anticoagulants in the prevention of the white thrombus, the efficacy of both coumarin agents and heparin in the prevention of the red thrombus, and the selective efficacy of heparin in the treatment of the disseminated intravascular coagulation syndrome — emphasize once again the differing pathophysiologic lineage of each of these forms of thrombosis (Table 1).

Summary

In summary, this report has considered in detail the normal hemostatic mechanism as a balanced concert of forces that leads to local hemostasis without tissue ischemia. Three forms of thrombosis have been presented, each postulated to arise from a different abnormality within the hemostatic system. Each represents a different balance between systemic and local factors and each has a characteristic response to anticoagulant therapy. The white thrombus arises primarily as an abnormality of the interaction between circulating platelets and an abnormal vessel wall. It is found primarily on the arterial side of the circulation and represents a purely local disorder. Anticoagulant therapy has not been shown to be of benefit in prophylaxis of this disorder. The red thrombus, which is primarily a red cell and fibrin mass, is found exclusively in areas of retarded blood flow, usually adjacent to normal blood vessel walls. The red thrombus represents a combination of a systemic process, activation of the intrinsic coagulation mechanism, and a local process, stasis. Insofar as the red thrombus is mediated by the coagulation process, anticoagulant therapy has been shown to be of benefit. Finally, disseminated intravascular coagulation, the deposition of fibrin in small vessels throughout the body, is a consequence of coexisting disease and a systemic activation of the coagulation system. In this syndrome the local manifestations are exclusively secondary to the other disease processes. Heparin is the drug of choice in the treatment of this disorder. The differing response of each form of thrombosis to anticoagulant therapy emphasizes the varying pathophysiology of each form of thrombosis.

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